Experimental evidence for proarrhythmic mechanisms of antiarrhythmic drugs

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Abstract

The major limitation to antiarrhythmic drug therapy is the risk of arrhythmia promotion, or ‘proarrhythmia.’ This complication may be lethal, and greatly restricts the value of antiarrhythmic agents, particularly for arrhythmias without an intrinsic mortality risk, such as atrial fibrillation. In order for improved antiarrhythmic drug therapy to be developed, it is essential to understand the fundamental mechanisms that cause proarrhythmic reactions to antiarrhythmic drugs. The present article reviews the experimental evidence that has been obtained regarding the mechanisms of proarrhythmia. The evidence available provides important insights, and points to potential strategies for developing newer and safer antiarrhythmic compounds.

Keywords: Pharmacology; Ion channel blocker; Cardiac arrhythmia; Sodium channel blocker; Potassium channel blocker; Action potential duration; Early afterdepolarization; Ischemic heart disease

1. Introduction

All currently available antiarrhythmic drugs that act by altering cardiac electrical properties have the potential to induce proarrhythmia, defined as either the worsening of pre-existing arrhythmias or the induction of new forms of arrhythmia in a given patient. This proarrhythmic potential is the most important factor limiting the use of antiarrhythmic drugs today.

Proarrhythmic reactions can take a variety of forms, including an increased number of premature atrial or ventricular complexes, an increase in the ventricular response rate to atrial fibrillation or flutter, the induction or facilitation of sustained ventricular tachyarrhythmias, and the alteration of ventricular tachyarrhythmia properties such that they become very resistant to direct current electrical cardioversion. The most disturbing manifestation of proarrhythmia is one in which overt tachyarrhythmias may not even be evident, specifically, an increase in the mortality rate in treated patients. Table 1 lists eight studies which point towards an increased mortality risk with antiarrhythmic drug therapy. Four studies examined patients after myocardial infarction (MI), three studied patients with atrial fibrillation (AF) and one evaluated empiric therapy in survivors of cardiac arrest. In many studies, sudden and/or presumed arrhythmic death rates were responsible for increases in mortality, pointing directly to proarrhythmic mechanisms. Drugs involved include members of classes Ia, Ib, Ic and III.

Data of the type shown in Table 1 are of prime concern for the use of antiarrhythmic drugs, particularly when drug therapy targets an arrhythmia like AF which is rarely lethal on its own. The development of improved antiarrhythmic therapy, with minimal or absent risks of proarrhythmia, depends in large measure on a detailed understanding of the mechanisms by which antiarrhythmic drugs induce proarrhythmic reactions. The purpose of the present paper is to review the experimental literature dealing with potential mechanisms of drug proarrhythmia.

2. Proarrhythmic mechanisms related to Na+ channel blockade

The ability of antiarrhythmic drugs to induce malignant tachyarrhythmias has been well recognized since the classic report of quinidine syncope by Selzer and Wray in 1964 [9]. Quinidine is classified as a class Ia antiarrhyth-
Table 1
Evidence for increased mortality in patients treated with antiarrhythmic drugs

<table>
<thead>
<tr>
<th>Study</th>
<th>Population/design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAST [1]</td>
<td>Randomized prospective comparison of placebo, flecainide and encainide in post-MI patients with PVCs.</td>
<td>Increased total and sudden death mortality with flecainide and encainide.</td>
</tr>
<tr>
<td>IMPACT [3]</td>
<td>Randomized prospective trial of mexiletine vs. placebo in post-MI patients with PVCs.</td>
<td>Increased mortality with mexiletine.</td>
</tr>
<tr>
<td>Flaker et al. [6]</td>
<td>Retrospective analysis of data from SPAF trial.</td>
<td>Excess mortality for AF patients with heart failure receiving antiarrhythmic drugs. No difference in absence of heart failure.</td>
</tr>
<tr>
<td>Nattel et al. [7]</td>
<td>Analysis of data from controlled trials of drug therapy of AF.</td>
<td>Increased mortality with quinidine, disopyramide, flecainide, and sotalol.</td>
</tr>
<tr>
<td>Moosvi et al. [8]</td>
<td>Retrospective analysis of empiric therapy for cardiac arrest patients.</td>
<td>Increased rate of recurrent cardiac arrest in patients receiving empiric quinidine or procainamide.</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; PVCs = premature ventricular complexes; AF = atrial fibrillation; SPAF = stroke prevention in atrial fibrillation.
mic drug [10], possessing both conduction-slowing actions due to Na\(^+\) channel blockade and an ability to prolong action potential duration (APD). With the advent of class Ic drugs in the early 1980s, it became apparent that these strong Na\(^+\) channel blockers are prone to produce particular forms of proarrhythmia, presumptively related to the facilitation of re-entrant arrhythmias by excessive conduction slowing [11–13]. Organic heart disease, particularly in association with coronary artery disease, was found to be an important risk factor for class Ic proarrhythmia [14].

2.1. Studies of class I drug proarrhythmia in the presence of prior myocardial infarction

In the light of the proarrhythmic response in post-MI patients suggested by the CAST study [1], it was natural to study potential proarrhythmic mechanisms in animals with prior MI. Limited early studies of class I drugs in dogs with prior MI showed occasional proarrhythmic reactions related to strong conduction slowing in the ischemic zone [15–17]. Kidwell and Gonzalez showed that D-sotalol was much more effective than flecainide in suppressing the induction of ventricular tachycardia (VT) in dogs with prior MI, and that flecainide was particularly likely to promote VT induction among dogs without inducible VT at baseline [18]. Wallace et al. showed that encainide caused dose-related promotion of VT induction in dogs with prior MI, allowing VT to be induced in a total of 6 of 10 dogs without inducible VT at baseline [19].

Three studies published in 1995 used epicardial mapping techniques to determine in detail the mechanisms by which flecainide promotes VT in dogs with prior MI [20–22]. All three studies showed that preferential conduction slowing in the ischemic zone facilitated the occurrence of circus movement tachycardia, with block or very slow conduction in the direction transverse to fiber orientation causing re-entry. In one study [21], unidirectional block was present during stimulated extrasystoles prior to flecainide, but the recirculating impulse encountered refractory tissue and failed to re-enter. Flecainide permitted the induction of sustained VT by slowing conduction in the ischemic zone enough to allow the recirculating impulse to re-enter. In a second study, unidirectional block was absent prior to the drug, which caused rate-dependent localized transverse conduction block and allowed for the spontaneous or induced occurrence of stable macrore-entrant VT oriented around a line of functional block parallel to longitudinal fiber direction [20]. In the latter study, flecainide rarely induced proarrhythmia in dogs without MI, and infarct size was an important determinant of proarrhythmia. The third study showed that flecainide caused VT either by inducing new arcs of transverse conduction block or by slowing conduction around a pre-existing arc of block to allow re-entry [22]. In all three studies, flecainide affected longitudinal and transverse conduction in normal tissue to a similar extent, and prominent effects on propagation in the infarct zone with limited or no effects on refractoriness created the basis for re-entry. Fig. 1 illustrates the induction of VT in the presence of flecainide and prior MI (as studied by epicardial mapping) in a dog in which no arrhythmia could be induced in the absence of the drug.

2.2. Class I proarrhythmia in the presence of acute myocardial ischemia

Acute myocardial ischemia produces a variety of important electrophysiological derangements, including particularly profound alterations in excitability and impulse propagation, that greatly predispose to malignant ventricular tachyarrhythmias [23,24]. In the late 1970s, Elharrar et al. showed that an early class Ic drug, aprindine, increased ischemia-induced conduction delay and appeared to increase the incidence of acute ischemic arrhythmias upon left anterior descending coronary artery (LAD) ligation in the dog [25]. A subsequent study showed that the administration of aprindine prior to LAD ligation resulted in substantial drug concentrations in the ischemic myocardium and significantly increased the prevalence of ischemic ventricular fibrillation (VF) from 14 to 49% [26]. No arrhythmogenic effect was noted for aprindine administered after coronary artery ligation, apparently because of very limited drug distribution into the ischemic myocardium at the time of maximal VF risk, and the same dose of aprindine given 24 h after acute MI suppressed ventricular ectopy [26]. These studies highlighted the important proarrhythmic potential of potent class I drugs when present in sufficient concentrations in the acutely ischemic myocardium, and suggested the possibility of an increased risk of ischemic VF in patients with coronary disease taking such drugs [26].

Later studies confirmed that a variety of other class I drugs administered prior to experimental acute MI also increase the risk of ischemic VF. Carson et al. showed that lidocaine administration increases the incidence of VF during subsequent coronary artery ligation in the pig [27], with rate-dependent drug-induced conduction depression during VT promoting degeneration to VF [27]. Subsequent studies confirmed the propensity of lidocaine administered prior to coronary artery occlusion to promote ischemic VF [28], and indicated that flecainide also increases the likelihood of ischemic VF when administered prior to the induction of acute myocardial ischemia [29,30]. There is a great deal of evidence which suggests that class I drugs promote ischemic VF by their effects on cellular excitability and impulse propagation [25,27,31–33]. It has also been suggested that spatially heterogeneous effects on action potential repolarization may result from the combination of acute ischemia and Na\(^+\) channel blockade, and contribute significantly to the genesis of ventricular tachyarrhythmias [34]. In the latter study, flecainide effects on APD and proarrhythmia occurred at relatively high concentrations (10–20 \(\mu\)mol·L\(^{-1}\)).
2.3. Class I proarrhythmia in the absence of myocardial ischemia or infarction

In contrast to the clear experimental information about class I proarrhythmia mechanisms in the setting of acute or chronic MI, much less is known about proarrhythmia in the absence of MI, particularly in normal hearts. Amitriptyline, a tricyclic antidepressant with anticholinergic and \( \text{Na}^+ \) channel-blocking properties, causes dose-related ventricular proarrhythmia in dogs which is related to an interaction between anticholinergic sinus tachycardia-inducing and ventricular conduction-slowing properties [35,36]. An abstract suggested that flecainide infusion causes a high incidence of ventricular proarrhythmia in anesthetized dogs [37], but a subsequent controlled study showed a low incidence of flecainide proarrhythmia in...
normal dogs over the full range of doses tolerated [20]. Several antiarrhythmic drugs increase the vulnerable window for arrhythmia induction in isolated guinea pig right ventricular strips [38], in keeping with mathematical simulations of the effect of Na\(^+\) channel blockade on ventricular vulnerability to arrhythmia induction [32,33]. These data suggest that, while class I drugs may cause proarrhythmia in the absence of cardiac pathology, the incidence is lower and the mechanisms less clear than in the setting of acute or previous MI. They are in keeping with the important clinical role of organic heart disease in predisposing to class I proarrhythmia [14].

Relatively little experimental work has been performed to address proarrhythmic potential of antiarrhythmic drugs in heart disease models unrelated to coronary artery disease. Brugada et al. showed that flecainide promotes the induction of sustained ventricular tachyarrhythmias in Langendorff-perfused rabbit hearts with a nearly transmural right ventricular endocardial cryolesion that leaves a thin layer of surviving epicardium [39]. The underlying mechanism resembled that of proarrhythmia with prior MI, in involving drug-induced promotion of a functional arc of conduction block.

2.4. Clinical relevance of experimental work on class I proarrhythmia

The experimental literature suggests that class I drugs produce predictable proarrhythmia in the presence of myocardial infarction, with somewhat different mechanisms operative in acute MI compared to prior infarction without acute ischemia. These data are consistent with the particular sudden death risk of patients with coronary artery disease exposed to class I drugs [1–3,14]. It is reasonable to wonder whether the experimental data can provide insights into the relative importance of the arrhythmogenic substrate presented by a healed myocardial infarction compared to that of acute myocardial ischemia. Based on an analysis of the literature, it has been suggested [40] that acute ischemia may be the central factor promoting class I drug-associated mortality in studies like CAST. This speculation is supported by an analysis of non-fatal ischemic events and sudden death in CAST [41], which found that patients treated with encainide or flecainide had the same number of endpoint events as placebo-treated patients when non-fatal ischemic events and sudden death were combined as endpoints. The excess of sudden death in drug-treated patients was accounted for by a reduced presentation of non-fatal ischemic events, suggesting that encainide and flecainide complicated what would otherwise have been non-fatal acute myocardial ischemia by causing lethal ischemic arrhythmias.

The importance of acute ischemic events is also suggested by an analysis of the concentration-dependence of flecainide proarrhythmia in dogs with acute vs. healed MI. Flecainide proarrhythmia in dogs with healed myocardial infarction has been reported at mean concentrations from 0.8 to 5.6 mg/L (2–14 \(\mu\)mol·L\(^{-1}\)) [18,20–22]. These concentrations are generally higher than the accepted therapeutic range of 0.2 to 0.7 mg/L (0.5–1.7 \(\mu\)mol·L\(^{-1}\)) [42]. Proarrhythmic events, particularly sustained VT, are more common at flecainide concentrations in the toxic range [13], and the facilitation of re-entry in the presence of a prior MI is likely to be important in this form of proarrhythmia. On the other hand, the excess mortality in CAST occurred at flecainide doses unlikely to produce toxic concentrations, and presented as sudden cardiac death rather than sustained VT. We have compared directly the concentration dependence of flecainide proarrhythmia in dogs with previous MI vs. dogs exposed to acute myocardial ischemia [43]. The acute ischemia model consisted of 10-min occlusions of the LAD separated by 30 min of reperfusion, which we have shown to result in a reproducible prevalence of ventricular tachyarrhythmias during each ischemic episode [44]. Dogs with previous MI were subjected to programmed electrical stimulation before and after successive loading and maintenance doses of the drug [20]. Proarrhythmia occurred in 79% of dogs with previous MI and 55% of dogs with acute ischemia. The concentration-dependence of flecainide proarrhythmia is shown in Fig. 2, and indicates that flecainide proarrhythmia occurred at therapeutic concentrations in dogs with acute MI (EC\(_{50}\) of 0.75 \(\mu\)mol·L\(^{-1}\)), concentrations that were 20-fold lower than those producing proarrhythmia in the setting of healed infarction without acute ischemia (EC\(_{50}\) 17 \(\mu\)mol·L\(^{-1}\)). Furthermore, flecainide proarrhythmia in acute MI generally presented as ventricular fibrillation, whereas with healed MI proarrhythmia presented as inducible sustained VT. These findings point to an interaction between flecainide and acute myocardial ischemia as a more likely candidate mechanism for the CAST findings than an effect on a healed MI substrate without superimposed ischemia.

The experimental literature provides limited information about proarrhythmia in the absence of structural heart disease. The data available suggest that proarrhythmia is
much less common in normal hearts than in hearts with myocardial infarction [20], but that proarrhythmia can occasionally occur in apparently normal hearts [20,32,33,38]. These findings suggest that there is less risk of proarrhythmia with class I drugs in patients with a low risk of heart disease, but that caution is still necessary. Even less experimental information is available about proarrhythmic risks and mechanisms of class I drugs in heart disease models other than those involving myocardial ischemia. Whereas it is likely that proarrhythmia would be favored by non-ischemic heart disease, further work will be necessary to quantify the relative risk and to establish underlying mechanisms.

3. Proarrhythmia related to action potential prolongation

In 1964, Selzer and Wray reported the occurrence of ventricular tachyarrhythmias as a complication of quinidine therapy [9]. The cases they described manifested marked QT interval prolongation and had recurrent syncope due to rapid, polymorphic ventricular tachyarrhythmias which they considered to be self-terminating ventricular fibrillation. It was subsequently recognized that the arrhythmias described by Selzer and Wray were a typical form of polymorphic VT caused by antiarrhythmic drugs that prolong the QT interval, commonly referred to as ‘Torsades de Pointes’ after the term coined by Desertennes in 1966 [45]. The association of Torsades de Pointes (TdP) arrhythmias and abnormal QT prolongation came to be known as the ‘acquired long QT syndrome’, and is recognized to occur as a complication of therapy with antiarrhythmic drugs that prolong the QT interval in about 1–3% of cases [46,47]. All class Ia and class III antiarrhythmic drugs can cause TdP arrhythmias in association with the long QT syndrome, whereas the latter occur rarely, if at all, with class Ib or Ic antiarrhythmic agents.

3.1. Cellular studies of the basis of the drug-induced acquired long QT syndrome

The acquired long QT syndrome has a number of highly characteristic features which provide clues about underlying mechanisms. The QTU interval is markedly prolonged, often ending with very large U waves, and the occurrence of the syndrome is facilitated by hypokalemia, hypomagnesemia, bradycardia, and drugs that prolong the action potential. Dangman and Hoffman showed in 1981 that N-acetylprocainamide, an active APD-prolonging metabolite of procainamide, caused early afterdepolarizations (EADs) during phase 3 of prolonged Purkinje fiber action potentials, as well as proarrhythmic ventricular ectopy in intact dogs [48]. In 1983, Brachmann et al. showed that bolus intravenous administration of the K⁺ channel blocker Cs⁺ to dogs caused bradycardia, marked QT interval prolongation and ventricular tachyarrhythmias [49]. In vitro studies demonstrated that Cs⁺ caused bradycardia-dependent EADs in canine cardiac Purkinje fibers, and Brachmann et al. suggested that EADs are responsible for the abnormal U waves and TdP arrhythmias in the drug-induced long QT syndrome [49]. Subsequent work showed that quinidine caused typical EADs in canine Purkinje fibers, which were favored by many of the known facilitators of the acquired long QT syndrome, including slow activation rates, hypokalemia, and hypomagnesemia [50–52]. The pharmacologic response of quinidine-induced EADs suggested that L-type Ca²⁺ current (I镧) was central in generating the upstroke of the EAD [51]. Microelectrode mapping was performed in one of the studies [51], and showed that EADs arose from Purkinje fibers and propagated to normally repolarizing ventricular muscle (Fig. 3). Based on this information, on the uncommon degeneration of TdP to ventricular fibrillation and on the relatively slow intrinsic frequency of quinidine-induced EADs, it was suggested that TdP may
result from the induction of intraventricular re-entry by EADS arising in Purkinje fibers rather than from a purely triggered mechanism in which EADS directly produce each of the ectopic beats of polymorphic TdP VT [51]. Quinidine has also been found to produce spatial and temporal APD heterogeneity in the ventricle, which could contribute to the induction of re-entry by EADS [53].

The development of EADS in Purkinje fibers may account for the origin of TdP, but it is unlikely that the very small mass of Purkinje fibers could produce the large U waves typically observed in patients with the long QT syndrome. Sicouri and Antzelevitch have demonstrated the presence of a large population of ventricular muscle cells (which they designated ‘M cells’) in the deep subepicardium with APD behavior resembling that of Purkinje fibers [54]. Unlike typical ventricular muscle cells, M cells readily display EADS upon exposure to drugs like quinidine, and are alternate or additional candidates to Purkinje fibers for the site of origin of EADS that cause TdP arrhythmias in the acquired long QT syndrome [55].

3.2. Experimental studies of the drug-induced long QT syndrome in intact hearts

Following the publication of Brachmann et al. [49], many groups used Cs⁺ administration to produce an in vivo model of the acquired long QT syndrome. A catheter technique to record monophasic action potentials was applied and suggested that Cs⁺-induced EADS could be recorded in vivo and had features consistent with a role in ventricular arrhythmogenesis and with the properties of EADS recorded in vitro [56–58]. In agreement with the response of quinidine-induced EADS in vitro [51], a variety of agents were found to suppress Cs⁺-induced EADS and/or ventricular arrhythmias in vivo, including Mg²⁺ [58,59], diltiazem [59], β-blockers [57,59] and Na⁺ channel blockers [59]. Sympathetic nerve stimulation enhanced [57], while vagal nerve stimulation suppressed [59,60], Cs⁺-induced EADS and/or ventricular arrhythmias. The application of the monophasic action potential catheter technique allowed for the recording of EADS in a patient with a quinidine-induced long QT syndrome, providing direct evidence for a role of EADS in the drug-induced long QT syndrome in man [61].

While many of the properties of Cs⁺-induced arrhythmias in vivo resemble those of the long QT syndrome, there is evidence that Cs⁺ can produce VT with properties quite different from those of the long QT syndrome, including monomorphic morphologies, overdrive enhancement and a tendency to degenerate to ventricular fibrillation [60,62]. Several animal models have been developed more recently in which antiarrhythmic drugs that produce TdP in man are used to cause a long QT syndrome. Dogs with chronic AV block develop typical QT prolongation and TdP arrhythmias upon exposure to quinidine and sotalol, but not propranolol, flecainide or lidocaine [63]. The occurrence of TdP can be enhanced by diuretic-induced hypokalemia [64] or by selective pacing protocols [65]. In agreement with the idea that EADS cause the drug-induced long QT syndrome, EADS are readily recorded in association with TdP caused by β-sotalol in vivo [65], and increased heart rate can suppress ventricular arrhythmias in the dog model [66]. Rabbits appear to be particularly prone to the long QT syndrome and TdP, and an anesthetized rabbit model has been developed which shows EADS, TdP and marked QT prolongation in response to a variety of agents that can produce long QT syndrome in man [66]. There is evidence in both rabbit [67] and dog models [68] for heterogeneity in repolarization as playing a particularly important role in the generation of TdP.

A number of studies have attempted to define the mechanisms of the classical TdP morphology associated with the drug-induced long QT syndrome. Bardy et al. used a combination of quinidine (30 mg/kg), myocardial ischemia and burst pacing to induce arrhythmias with a TdP morphology in dogs on cardiopulmonary bypass [69]. Epicardial mapping with 27 electrodes suggested that TdP was caused by two or more competing epicardial activation sequences. In a study using similar techniques to induce TdP (30 mg/kg of quinidine, aggressive programmed stimulation with up to four extrastimuli) and 38-electrode mapping, Inoue et al. concluded that TdP resulted from alterations in activation pattern rather than competing foci of activation [70]. These studies were limited by the conditions used to create TdP, which differed greatly from the conditions of the drug-induced long QT syndrome in man, and from the very limited tools used to study underlying mechanisms. El-Sherif et al. showed that the Na⁺ channel agonist anthopleurin-A (AP-A) causes arrhythmias resembling those of the acquired long QT syndrome in anesthetized dogs, along with EADS in canine Purkinje fibers in vitro [71]. They subsequently performed three-dimensional mapping of AP-A induced VT with the use of 192 bipolar recordings in anesthetized puppies [72]. The first beat of VT resulted from focal activity in the subendocardium, compatible with an origin in the Purkinje fiber network, and subsequent activity was due to repeated focal subendocardial activity, re-entry triggered by the initial subendocardial focus, or a combination thereof. The polymorphic morphology of VT was due to shifting sites of activation or varying orientations of circulating wavefronts. Asano et al. used high-resolution optical mapping (up to 40,000 pixels) to study quinidine-induced TdP in a rabbit model [73]. Polymorphic VT was found to be due to changes in wave propagation patterns for successive beats initiated by EADS or EAD-induced non-stationary re-entrant activity. The results of the latter study are consistent with modeling work which showed that reductions in K⁺ permeability can increase APD and cause premature beats to initiate non-stationary spiral wave activity resulting in TdP-like ECG morphologies [74].
3.3. Insights into molecular mechanisms from advances in understanding the molecular basis of the congenital long QT syndrome

The congenital long QT syndrome shares a variety of features, including marked QT prolongation and TdP VT morphology, with proarrhythmia caused by APD-prolonging antiarrhythmic drugs [47]. Understanding of the molecular basis for the congenital syndrome has exploded with the recent characterization of the genetic mutations responsible for the majority of cases [75–77]. Three specific ion channel abnormalities have been defined, a defect in HERG, a gene on chromosome 7 which encodes the rapid component of the delayed rectifier $I_{K_r}$ [78]; mutations in SCN5A, a gene on chromosome 3 which encodes the cardiac Na$^+$ channel $\alpha$-subunit, that result in incomplete $I_{Na}$ inactivation [79,80]; and an abnormality in K$_r$, LQT1, a gene on chromosome 11 that encodes a major subunit of the slow delayed rectifier $I_{K_s}$ [81,82]. Many antiarrhythmic drugs that cause TdP have $I_{K_s}$ blockade as a prominent ionic action. Recent work shows that drugs that cause TdP produce high-affinity block of HERG channels expressed in Xenopus oocytes [83–85]. Thus, drug-induced long QT syndrome appears to be an iatrogenic reproduction of a congenital, potentially lethal disease. The specific clinical features of the syndromes due to abnormalities of K$_r$, LQT1 (LQT1), HERG (LQT2) and SCN5A (LQT3) remain to be defined, and may provide additional insights into the mechanism of acquired long QT syndromes. In addition, it remains to be determined whether clinically used drugs can also cause TdP by inhibiting $I_{K_s}$ (like LQT1) or interfering with inactivation of $I_{Na}$ (like LQT3), and if so, how the manifestations of proarrhythmia due to such agents may differ from those of $I_{K_s}$ blockers. The identification of the role of HERG and K$_r$, LQT1 in $I_{K_s}$ and $I_{K,a}$, respectively, allows for detailed analyses of molecular mechanisms of drug action that were impossible previously, and will hopefully lead to opportunities to develop drugs with improved antiarrhythmic efficacy and/or reduced proarrhythmic potential.

3.4. Potential clinical role of proarrhythmia by action potential-prolonging drugs in the presence and absence of excessive QT prolongation

The importance of proarrhythmia related to delayed repolarization as a cause of sudden cardiac death may be underestimated. In a study of patients with the arrhythmic mechanism of sudden death recorded during ECG monitoring, Hohnloser and Meinertz noted that 20% had TdP as a terminal arrhythmia and 70% of these were taking antiarrhythmic drugs [86]. Furthermore, 55% of all recorded sudden-death patients had marked QT prolongation and 60% of these were on antiarrhythmic drugs. These findings suggest that drug proarrhythmia may have been involved in a substantial number of cases of sudden cardiac death.

Class III antiarrhythmic drugs are particularly likely to produce EADs in Purkinje fibers surviving in a region of myocardial infarction [87]. Such regional EADs might result in VT without prolongation of the QT interval or the typical features of TdP, and could underlie the increased mortality risk of post-MI patients treated with d-sotalol in the SWORD trial [4]. Patients with congestive heart failure are predisposed to sudden cardiac death, the underlying mechanisms of which are uncertain [88]. Ventricular action potential prolongation is a consistent feature of animal models of congestive cardiomyopathy [89,90]. It is thus quite possible that patients with heart failure are predisposed to EADs and to drug-induced TdP. This concept is consistent with the important mortality risk of patients with heart failure and AF exposed to antiarrhythmic drugs in the SPAF trial [6], and raises the possibility that some of the sudden death mortality in patients with heart failure may be due to the antiarrhythmic drug therapy of ventricular arrhythmias, rather than despite it.

4. Prevention of proarrhythmia and implications for antiarrhythmic drug therapy

It is clear that the major limitation to antiarrhythmic drug therapy today is the risk of serious proarrhythmia. It is further clear that, unless new approaches are developed to prevent proarrhythmia, the use of antiarrhythmic drugs is likely to continue to decrease in the future. Therefore, the major challenge in antiarrhythmic drug development is to discover new agents that are effective antiarrhythmics with greatly reduced or absent risks of proarrhythmia.

4.1. Cellular and ionic considerations

The proarrhythmic risk of Na$^+$ channel blockers is related to the important excitability-reducing effects they have in acutely ischemic tissue. Since acute ischemia tends, if anything, to enhance drug-induced $I_{Na}$ inhibition [31], it is unclear at the moment whether class I drugs can be developed with reduced proarrhythmic potential. Drugs that prolong APD appear to produce arrhythmogenic EADs by causing bradycardia-dependent APD prolongation in Purkinje fibers. In order to produce antiarrhythmic APD prolongation without a significant risk of proarrhythmia, drugs would have either to target ion channels that are absent in Purkinje fibers or to prolong APD only during rapid tachyarrhythmias.

4.2. Possible approaches to developing antiarrhythmic drugs with reduced proarrhythmic potential

Widespread application of the patch-clamp technique has provided important new insights into the ionic mechanisms governing repolarization in various tissues. Furthermore, the cloning of channel subunits allows for better understanding of the molecular mechanisms of ion channel function as well as for rapid screening of blocking drugs in...
model systems that express channels of interest. It has been found that a particular K⁺ current, the ultrarapid delayed rectifier \( I_{Ku} \), plays an important role in human atrial repolarization [91] and is absent in human ventricle [92]. It remains to be determined whether \( I_{Ku} \) is present in human Purkinje fibers, but if not, selective \( I_{Ku} \) blockers may control atrial arrhythmias with minimal risk of ventricular proarrhythmia.

A second possible approach is to develop drugs that increase APD only during tachycardia, with little or no effect at sinus rates. Computer-assisted methods to developing drugs with improved rate-dependence of APD prolongation have been described [93], but no clear success has yet been reported. K⁺ channel blockers have time- and state-dependent interactions with K⁺ channels [94–96]. It is possible that advances in molecular pharmacology will permit the development of state-dependent K⁺ channel blockers that produce block only during pathological tachycardias. An alternative approach is to target K⁺ channels that are particularly important at rapid rates. Jurkiewicz and Sanguinetti have suggested that \( I_{Ku} \) is such a channel, and that \( I_{Ku} \) blockers may have a superior profile of APD-prolonging action [97]. There is some experimental evidence for this contention [98,99], but contrary findings have been published as well [100]. The finding that mutations in an essential subunit of \( I_{Ku} \) are responsible for one of the congenital long QT syndromes (LQT1) [81,82] suggests that \( I_{Ku} \) inhibition may not be a straightforward strategy to develop an effective antiarrhythmic with reduced proarrhythmic potential.

5. Conclusions

Experimental findings have provided great insights into the mechanisms underlying proarrhythmic reactions to antiarrhythmic drugs. They have also provided clues which may be helpful in developing antiarrhythmic agents with reduced proarrhythmic potential. The introduction of safer antiarrhythmic drugs is essential if drug therapy is to be a significant part of the approach to treating cardiac arrhythmias in the rapidly approaching next millennium.

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